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STUDIES OF PROTONATION OF SOME AMINOPOLYCARBOXYLATES BY CARBON-13 NMR SPECTROSCOPY

BY

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ABSTRACT

^{13}C nmr chemical shifts are used to evaluate successive protonations of the aminopolycarboxylate systems diethylenetriaminepentaacetic acid (DTPA) and triethylenetetraminehexaacetic acid (TTHA).

INTRODUCTION

Proton nmr spectroscopy has been used by a number of groups to study the protonation sequence of aminopolycarboxylates. Letkeman and Martell have reported the results of their study of molecules containing from two to six nitrogen atoms.[2] Their estimates of the fractional protonation of possible sites after the addition of each equivalent of base is in fair agreement with the earlier values of Sudmeier and Reilley for EDTA (ethylenediamine tetraacetic acid) and DTPA (diethylenetriaminepentaacetic acid).[3]

These studies have measured the shifts of methylenic protons which are several bonds from the protonation site. Not only are carbon

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atoms closer to these basic sites but the range of intrinsic ^{13}C shifts is an order of magnitude greater than that of ^{1}H shifts. Consequently ^{13}C shift variation with pH could provide a more sensitive method to study protonation sequences in these multi-basic systems. This and other advantages of ^{13}C vs ^{1}H spectroscopy in such studies have been discussed by Reilley and coworkers.[4] This group as well as Jezowska-Trzebiatowska, et al., have used ^{13}C shifts to study protonation of DTPA.

In this paper we report the results of our investigation by ^{13}C nmr of the protonation of EDTA, DTPA, and TTHA (triethylenetetramine-hexaacetic acid).

EXPERIMENTAL

EDTA and DTPA were obtained from Aldrich Chemical Co., Milwaukee, WI. TTHA was purchased from ICN Pharmaceuticals, Inc., Plainview, NY. All the acids were used without further purification since the nmr spectra of the acids indicated acceptable purity for our purposes.

Proton-decoupled ^{13}C nmr spectra were obtained at a field of 6.34 Tesla (67.9 MHz) on a quadrature detection Bruker HX-270 spectrometer. Measurements were made using 13 mm sample tubes containing 5-6 ml of either 0.25M or 0.5M aqueous solution of the acids (1 ml D_2O was used for field/frequency lock purposes). All experiments were conducted at the ambient temperature of 29°C. Depending on the concentration of solution, either 32 or 64 pulses were accumulated, as 8192 point free induction decays. Prior to Fourier transformation, a 2 Hz line broadening was used for signal/noise enhancement. Dioxane was used as internal reference (set equal to 67.40 ppm; chemical shifts are reported with respect to TMS).

A Beckman model 1019 pH meter equipped with a Thomas 1/4 inch diameter (0-12 pH range) combination glass electrode was used for all

pH measurements. The pH meter was calibrated at 25°C with both pH = 7 and pH = 4 standard buffers.

RESULTS AND DISCUSSION

The variation of chemical shifts of carbon atoms with pH in DTPA and TTHA are shown in Figures 1 and 2 respectively (the determination for EDTA is not shown). The labeling scheme is shown on the molecular formulas included in each figure. The successive pKa values of each acid are indicated also.

The patterns of the shifts of each of the three acids are rather similar to those of the analogous protons. We follow the procedure of Letkeman and Martell[2] to calculate the fractional protonation of each site after addition of each equivalent of acid. δ_A is defined as the

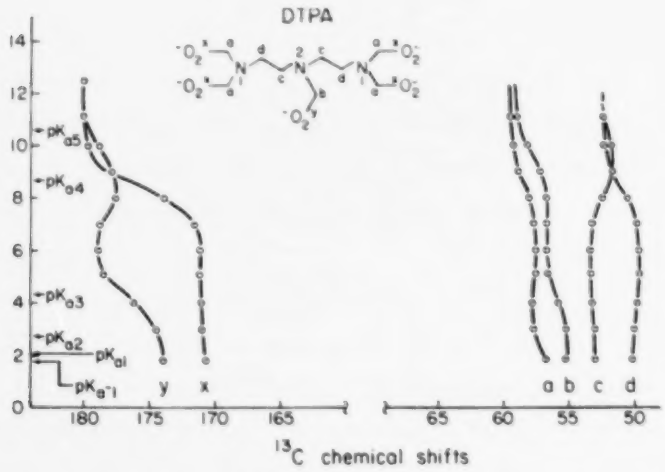

Figure 1. Variation of ^{13}C nmr chemical shifts for DTPA as a function of pH.

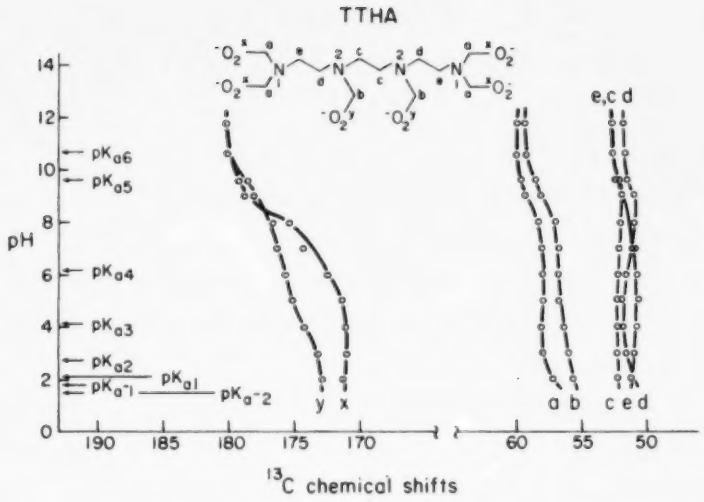

Figure 2. Variation of ^{13}C nmr chemical shifts for TTHA as a function of pH.

shift of any particular carbon when the nitrogen sites are fully protonated (pH $\geq$ 2.5) and δ_B as the shift in the completely deprotonated form (pH $\geq$ 12). From the observed shift, δ_i, for a particular carbon at any pH, the fractional protonation, f_i, of the nitrogen perturbing that carbon can be calculated:

$$f_i = (\delta_i - \delta_B)/(\delta_A - \delta_B)$$

Moreover, the sum of the fractional protonation of all nitrogens equals n, the number of equivalents added. Inflection points occur where $\delta_i = 1/2(\delta_A - \delta_B)$ which corresponds to the condition pH = pKa_n. This allows us to obtain δ_i values where there is a 50-50 mixture of $H_{n-1}Y$ and H_nY. Using the pKa values reported in reference 2, we calculated the

percentage of the different species as a function of pH. From these curves, we could choose δ_i values from Figures 1-2 which correspond to a single species. In some cases, it was necessary to correct for the presence of small amounts of another species. We used only the carbons of the carboxylate groups (x and y in Figures 1-2) as the shifts were greater for these. The results of our estimates of f_i are presented in Table 1.

The values in Table 1 calculated from carbon-13 shifts can be compared with those of reference 2 calculated from proton shifts. In

TABLE 1

Fractional Protonation of Different Nitrogen Atoms

n	f_i	f_2	$\Sigma f_i = n$
		EDTA	
1	0.43		0.9
2	0.99		2.0
		DTPA	
1	0.06	0.82	0.9
2	0.98	0.21	2.2
3	0.99	0.96	2.9
		TTHA	
1	0.1	0.2	0.6
2	0.56	0.50	2.1
3	0.93	0.68	3.1
4	1.0	0.95	4.0

the DTPA system, the results differ only for n = 1 where the proton data indicates $f_1 = 0.25$ and $f_2 = 0.50$. While these data imply that protonation of the central nitrogen is favored, the carbon shifts indicate it is protonated almost exclusively. In the TTHA system the results of the two studies are in rather good agreement (our n = 1 data is not reliable).

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